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Longitudinal associations of childhood internalizing psychopathology with substance misuse: A register-based twin and sibling study

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Key words: internalizing, externalizing, childhood, longitudinal, substance use

Abstract

Objective The pathways from internalizing psychopathology to substance misuse remain largely unclear. We estimated associations between childhood internalizing problems and subsequent substance misuse in two family-based samples. We also investigated sex differences and the role of externalizing comorbidity.

Method We studied associations of childhood internalizing psychopathology with register-based substance misuse after age 13. Sample 1 included all individuals born in Sweden 1984–2000 (N=1,768,516). Depressive and anxiety disorders were included as register-based ICD-9/10 diagnoses before age 13. Sample 2 was a sub-sample within the population sample, the Swedish CATSS twin cohort (n=12,408; born 1992–1998), with mood and anxiety problems assessed at age 9/12 by parents. In both samples, substance misuse was defined as an ICD-9/10 alcohol/drug use disorder or an alcohol/drug-related criminal conviction until December 2013. To account for familial effects, stratified analyses were conducted within siblings and twin pairs.

Results In the population sample, both depressive (HR=2.75 [95% CI: 2.36–3.20]) and anxiety disorders (HR=1.52 [1.35–1.73]) were associated with substance misuse. Childhood mood problems (HR=2.28 [1.69–3.08]) were associated with substance misuse in the CATSS sample. The associations were partially explained by familial factors, and comorbid externalizing disorders explained the associations in men but not in women.

Conclusion Childhood mood problems were associated with substance misuse but familial factors shared by siblings partially explained the associations. The relationship of anxiety with substance misuse was complex and depended on measurement and the type of anxiety disorder. Internalizing problems may be especially important for substance misuse risk in women.

Lay summary

In a study of two large community-based samples from Sweden, childhood depression and anxiety were associated an increased risk of subsequent alcohol or drug use problems. Depression was consistently associated with substance misuse whereas the relationship of anxiety with substance misuse was complex and depended on the measurement and the type of anxiety disorder. Depression was robustly associated with substance misuse in women only, which suggests that depression may be especially important for substance misuse risk in women. ADHD and conduct disorder symptoms co-occurring with depression and anxiety amplified the risk for substance misuse more in women than in men, possibly reflecting sex-specific mechanisms in the development of alcohol or drug use problems.

Clinical guidance

- Screening for mood-related problems may help to identify children who are at risk of developing substance misuse in adolescence or early adulthood.
- Mood-related psychopathology may be an important risk marker for substance misuse especially in women.
- In both primary care and specialist services, it is important to assess for internalizing disorders even if the primary reason for referral is a neuropsychiatric disorder (ADHD), as comorbid internalizing and externalizing psychopathology may be associated with an increased risk of alcohol or drug use problems.

Introduction

Substance use disorders (SUDs) are associated with increased mortality as well as high economic costs and societal burden.[1,2] Other psychiatric disorders often precede the onset of SUDs, but much remains unclear about the longitudinal associations between childhood psychopathology and SUDs. [3,4] Previous literature suggests at least two distinct risk factors for SUDs: externalizing disorders characterized by behavioral disinhibition (i.e. ADHD, oppositional defiant disorder (ODD) and conduct disorder)[3] and an internalizing disorders leading to SUDs possibly through self-medication behaviors used to alleviate feelings of anxiety and depression.[4] There is consistent support for externalizing behaviors being associated with SUDs[5,6], but findings on internalizing disorders remain inconclusive.[7-9] A meta-analysis of longitudinal studies of children and adolescents found that depression, but not anxiety, was associated with the risk of subsequent SUDs.[7] Findings on sex differences are also mixed: there is some cross-sectional and longitudinal evidence for internalizing psychopathology being a greater risk factor for SUDs in women than in men[10,11], but some longitudinal studies report no sex differences.[12] The inconclusive results may in part reflect variability in the measurement of internalizing disorders; many studies are based on community samples using self-report measures while only a few studies have used clinical diagnoses, and the association may depend on the severity of depression and anxiety.[7]

It is also important to consider that SUDs and other psychiatric disorders have shared etiological factors such as genetic liability and environmental influences[13,14], which could give rise to the observed associations. Standard epidemiological study designs cannot rule out the possibility that an observed association between internalizing psychopathology and SUDs is explained by such shared underlying liabilities. Twin and family studies, however, can account for shared familial factors and provide more robust evidence of a direct association between internalizing psychopathology in childhood or adolescence and subsequent SUDs.[15]

Only a few studies have examined the association between childhood/adolescent internalizing psychopathology and subsequent alcohol or drug use with genetically informative designs, but to our knowledge, none have investigated diagnosed SUDs specifically. Childhood depression was associated with adolescent alcohol use, but not drug use, in a sample of Finnish twins whereas social anxiety at the age of 12 was not associated with subsequent drug use.[16,17] Another study conducted cross-sectional reciprocal causation twin modeling in the same data and concluded that there was inconclusive evidence for a causal path from childhood depression to adolescent alcohol use frequency.[18] A Swedish longitudinal study of adolescent twins found that the association of anxiety and depressive symptoms with intoxication frequency was mostly explained by individual-specific environmental factors[19], which is consistent with a possible causal relationship. In conclusion, there is some evidence that childhood/adolescent anxiety and depression are associated with alcohol use after familial factors are accounted for, but the findings are mixed and it remains unclear to what extent familial factors explain the association between internalizing psychopathology and SUDs.

There is a high degree of co-occurrence between internalizing and externalizing problems[20,21], but most prior research has focused on either internalizing or externalizing spectrum. Furthermore, the effect of their comorbidity on the risk of SUDs is not well understood. “Pure” externalizing psychopathology has been associated with a higher risk of subsequent alcohol and drug use in adolescents than comorbid externalizing and internalizing symptoms[22], but other longitudinal studies have found the highest risk among individuals with both internalizing and externalizing psychopathology.[23, 24] In two cross-sectional adolescent samples, comorbid depression and conduct disorder was associated with a higher risk of SUDs than would be expected considering only the effects of each disorder alone.[25,26] Further, a longitudinal study by Colder *et al*. suggested that in the absence of comorbid

externalizing behaviors, internalizing psychopathology was protective against substance use.[22] These results highlight the importance of taking comorbid externalizing psychopathology into account when investigating the association between internalizing psychopathology and SUDs.

To better understand the longitudinal association between internalizing problems and substance misuse, we investigated the association of childhood anxiety and mood-related problems with subsequent substance misuse in two prospective samples. First, in a large prospective twin sample linked with register data, we studied associations between parent-reported internalizing psychopathology and register-based substance misuse, and examined whether they are accounted by familial factors. Second, we investigated associations in the general population between register-based anxiety and depressive disorders diagnosed in childhood and subsequent substance misuse, and controlled for familial factors shared by full siblings. In both samples, we also studied the role of externalizing comorbidity and sex in the development of substance misuse.

Based on prior research, we expected to find a positive association between internalizing disorders and substance misuse. We further hypothesized the association to be at least partially explained by comorbid externalizing problems and familial factors. We did not have specific hypotheses concerning sex differences.

Methods

Samples

The Child and Adolescent Twin Study in Sweden (CATSS)

The Child and Adolescent Twin Study in Sweden (CATSS) is a longitudinal study aiming to recruit all twins born in Sweden since July 1st 1992.[27] From 2004 onwards, all 12-year-old (born 1992–1995) and 9-year-old (born July 1st 1995 and after) twins have been identified through the Swedish Twin Registry and their parents have been asked to participate in a telephone interview about their children's somatic and mental health. The response rate for the present sample was 76%, with the mother being the informant in most families.[27] The sample consists of 12,408 individuals born 1992–1998 whose parents participated in the age 9/12 interview. There were 1846 monozygotic (MZ), 2192 same-sex dizygotic (DZ), and 2043 opposite-sex DZ twin pairs. The data also included 103 pairs with unknown zygosity and 40 individuals without their co-twin in the study, who were included in the individual-level analyses. Zygosity was determined with 48 single nucleotide polymorphisms, or in case DNA information was not available, by an algorithm based on a questionnaire on twin similarity.[27] The CATSS study was approved by the Karolinska Institute Ethical Review Board, and parents provided consent for their children to participate.

Population sample

In the population sample, we included all individuals born in Sweden in 1984–2000 from the Total Population register (N=1,768,516). The CATSS twin cohort can be considered a sub-sample within the population sample. The population sample was linked to the National Patient Register (NPR)[28], the Cause of Death Register, the Migration Register, and the Multi-

Generation Register.[29] We used the Multi-Generation Register and the Swedish Twin Registry to identify full siblings and MZ and DZ twins, respectively. We excluded individuals whose parents could not be identified from the Multi-Generation Register (n=23,834), which is required for linking family members. The use of nationwide registers has been approved by the Regional Ethical Review Board in Stockholm. Informed consent requirement was waived because participants are not identifiable at any time.

Measures

CATSS: Internalizing and externalizing measures

In the CATSS sample, anxiety and mood problems, ADHD, and conduct disorder were assessed with the Autism - Tics, AD/HD and other Comorbidities Inventory (A-TAC), a validated instrument covering all common psychiatric disorders in child and adolescent psychiatry.[30] The A-TAC items are worded to assess DSM-IV symptoms and well known clinical phenomena. The parents were asked to rate their 9/12-year-old children on each symptom on a dimensional scale: 0 = item does not apply; 0.5 = applies to some extent; and 1 = applies in full. If the parent endorsed, fully or partially, at least one item as applying to their child, the interviewer proceeded to ask whether the symptoms had led to (1) dysfunction at school, among peers, or at home, and (2) suffering on the part of the child. A problem load score was then calculated as the sum of the two items on dysfunction and suffering (range 0-2), with a cut-off for problems to be considered significant at ≥ 1, indicating either that at least one of the problem questions was fully endorsed or that both were endorsed to some extent.[31]

Anxiety-related problems were assessed with the A-TAC based on items related to panic attacks, fears, general anxiousness, and social withdrawal. The A-TAC mood scale included

items related to e.g. depressed mood, feelings of worthlessness, lack of self-confidence, psychosomatic symptoms, and self-harm (see Table S1 for a list of the items, available online). For both anxiety and mood problems, we used a binary variable derived from the corresponding problem load score in order to capture cases with more severe or debilitating forms of psychopathology (coded: 0 = no problematic symptoms, 1 = problematic symptoms). The A-TAC scales on symptoms of ADHD, ODD, and conduct disorder were used as covariates in the primary analyses (continuous variables).

Population sample: Internalizing and externalizing measures

The population sample was linked to the NPR using the unique personal identity number assigned to each individual living in Sweden.[32] The NPR covers all inpatient (1973–) and outpatient (2001–) diagnoses with data available in the current study until December 31, 2013. We included ICD-9 and ICD-10 diagnoses of anxiety and depression (diagnosis codes listed in Table S2, available online) registered before age 13. We also included diagnoses of anxiety disorders with onset specific to childhood (i.e., separation anxiety disorder and childhood social anxiety disorder) registered before age 13. We included diagnoses of ADHD and conduct disorders as covariates. We also conducted a sensitivity analysis with autism as a covariate to control for a potential selection bias: for instance, children who received an anxiety/depression diagnosis might have been in the clinic primarily for neuropsychiatric assessment.

CATSS: Internalizing and externalizing comorbidity in childhood

To illuminate the consequences of externalizing comorbidity, we also investigated the role of comorbid internalizing and externalizing psychopathology on the risk of substance misuse.

An individual was classified as having internalizing psychopathology if the A-TAC symptoms exceeded the "significant impairment" cut-off (≥ 1) in the anxiety or mood problems scale. Externalizing psychopathology was defined as fulfilling the DSM-IV diagnostic symptom criteria for ADHD, ODD, or conduct disorder in the A-TAC (i.e., the continuous symptom count variable was categorized for these analyses). Each individual was classified as belonging to one of the following groups: 1) no psychopathology, 2) internalizing psychopathology only, 3) externalizing psychopathology only, 4) both internalizing and externalizing psychopathology.

Population sample: Internalizing and externalizing comorbidity in childhood

Similarly, we investigated the effect of externalizing comorbidity in the population sample. Internalizing psychopathology was defined as an ICD-9/10 diagnosis of anxiety or depressive disorder, or childhood specific anxiety disorder. Externalizing psychopathology was defined as an ICD-9/10 diagnosis of ADHD or conduct disorders (for diagnosis codes, see Table S2, available online). Each individual was classified to one of the following groups: 1) no psychopathology, 2) internalizing psychopathology only, 3) externalizing psychopathology only, 4) both internalizing and externalizing psychopathology.

CATSS and the population sample: Substance misuse

We studied substance misuse based on information from the nationwide Swedish registries by linking individuals in the two samples to the NPR and the Crime register. Substance misuse was defined as having an ICD-9/10 diagnosis of alcohol or drug use disorder or an alcohol/drug-related criminal conviction in the registries. The Crime Register includes district court convictions among people aged 15 and older since 1973, and follow-up was available

until December 31, 2013. Thus, the maximum age at the end of follow-up was 21 years in CATSS and 29 years in the population sample. To ensure that the study design was prospective, we studied substance misuse starting at age 13 and excluded individuals with substance misuse registrations before age 13 (CATSS n=17, register based sample n=733).

Analyses

CATSS and the population sample: Associations of childhood psychopathology and substance misuse

We used Cox proportional hazards regression, with age as the underlying time-scale, to estimate the effect of childhood anxiety and mood-related problems on the risk of subsequent substance misuse. The participants of both CATSS and the population-based sample were followed up through the nationwide registers from their 13th birthday until the date of first substance misuse event, emigration, death, or December 31, 2013, whichever occurred first. We accounted for the non-independence of observations in families by using a cluster-robust sandwich estimator for standard errors. Since men and women have a different prevalence of substance misuse, we allowed sex-specific baseline hazards and estimated all models stratified by sex. We also present separate coefficients for men and women. All models were adjusted for birth year, and the models including both men and women were also adjusted for sex.

CATSS and the population sample: Within-family analyses

Several factors may confound the association between childhood psychopathology and substance misuse. The association may be explained by 1) genetic factors, which are shared completely by MZ co-twins, and on average, 50% by DZ co-twins and full siblings, 2) environmental factors that are shared both by co-twins and siblings reared together, and 3)

non-shared environmental factors which make co-twins and siblings dissimilar. Stratified analyses within twin pairs and clusters of siblings can thus account for the contribution of unmeasured genetic and shared environmental factors.[33] We conducted within-family analyses with stratified Cox regression models within twin pairs in the CATSS sample and within clusters of full siblings in the population sample. A stratified model within full siblings accounts for all unmeasured genetic and environmental factors shared by siblings, and thus adjusts for 50% of genetic factors and all shared environmental factors. In addition, we stratified the models by sex to account for different baseline hazards in men and women, and we also report results from separate models for men and women.

CATSS and population sample: Internalizing and externalizing comorbidity in childhood

In both samples, we estimated associations of comorbid and non-comorbid internalizing and externalizing with substance misuse in Cox regression models, using the "no psychopathology" group as the reference category. Internalizing psychopathology only, externalizing psychopathology only, and both internalizing and externalizing psychopathology groups were compared to the no psychopathology group in terms of their relative risk of substance misuse. We present the estimates separately for men and women.

Results

Table 1 shows the distribution of internalizing and externalizing psychopathology in childhood, and register-based substance misuse since age 13 in the CATSS and population samples. The median age of first registered substance use disorder diagnosis or substance use-related criminal conviction was 17.2 in the CATSS sample and 18.4 in the population sample. In the population sample, substance use disorders were on average diagnosed earlier among those with anxiety/depressive disorders than among those with ADHD (Table S3, available online).

Associations of childhood anxiety and mood problems with subsequent substance misuse in CATSS

Childhood mood problems were associated with subsequent substance misuse (hazard ratio, HR=2.28 [95% CI: 1.69–3.08]) whereas the estimated association for anxiety-related problems was statistically non-significant (Table 2). Confidence intervals for the associations in men and women (HR=1.96 [1.34–2.90] vs. 2.97 [1.82–4.84]) were overlapping. When childhood symptoms of ADHD and conduct problems were accounted for, the association between mood problems and substance misuse was completely attenuated in men but remained evident in women.

Associations of childhood anxiety and depressive disorders with subsequent substance misuse in the population sample

Anxiety and depressive disorders registered before age 13 were associated with an elevated risk of subsequent substance misuse (Table 3). Childhood-specific anxiety disorders were

also associated with substance misuse but the estimate was imprecise and non-significant. As seen in Table 3, the associations were stronger in women than in men for both depression (HR=3.65 [2.86–4.64] vs. HR=2.35 [1.93–2.87], p=.006) and anxiety disorders (HR=1.77 [1.49–2.11] vs. HR=1.34 [1.12–1.59], p=.026), whereas no sex difference was found for childhood specific anxiety disorders (HR=1.55 [0.74-3.26] vs. HR=1.27 [0.72-2.23], p=.668). After adjusting for ADHD and conduct disorders, anxiety and depressive disorders were still associated with an elevated risk for substance misuse in women. In men, anxiety and depression were associated with a lower risk for substance misuse when adjusted for externalizing disorders. In within-family analyses, the HR for depression increased in men but attenuated in women. A similar trend was found for the association between anxiety disorders and substance misuse. As a sensitivity analysis, we further adjusted the models for autism (Table S4, available online), but there was little change in the estimates.

Internalizing and externalizing comorbidity in CATSS and the population sample

Having comorbid externalizing and internalizing problems seemed to be associated with an especially elevated risk for substance misuse in women in both samples. In contrast, no such pattern was present in men (Figure 1, Table S5; available online). However, especially in the CATSS sample, confidence intervals were overlapping.

Discussion

In two prospective family-based samples, we found consistent support for mood-related psychopathology being associated with an elevated risk of subsequent substance misuse, and for a different developmental pattern of substance misuse in men and women. Our study had notable strengths. First, we studied substance misuse as identified from nationwide registers, which rules out reporting biases common in studies of alcohol and drug use and problems. To capture a wider range of substance use problems, we included alcohol and drug related criminal convictions in addition to diagnoses of substance use disorders. Second, using two different samples, we assessed childhood anxiety and depressive disorders with parental reports of symptoms and with register-based diagnoses. The use of two complementary methods adds to the credibility of our findings. Third, both the twin cohort and register-based data enabled studying the role of comorbid externalizing problems, based on parental reports and registered diagnoses, respectively. Finally, both samples had data on siblings, allowing within-family analyses to investigate the contribution of familial liabilities.

We found that childhood mood problems were associated with an elevated risk of subsequent substance misuse, consistent with findings from earlier community-based studies.[7] The estimates for anxiety were imprecise, and the exact magnitude of elevated risk was thus unclear. In the population-based sample of nearly 2 million individuals in Sweden, both anxiety and depressive disorders in childhood were associated with an elevated risk of substance misuse. Childhood-specific anxiety diagnoses, i.e., separation anxiety and childhood social anxiety, were also associated with an increased risk of substance misuse. However, this association was reversed when accounting for comorbid externalizing disorders, in line with an earlier study.[22] Associations between different internalizing problems and substance misuse were similar across samples, although the hazard ratios were slightly higher in the population sample. Similar findings have been reported in previous

studies where the associations between SUDs and anxiety and depressive disorders were more elevated in register-based samples compared to community-based survey studies[34-36]. More elevated risks in studies using national patient registries may reflect the effect of more severe psychopathology on the risk of substance misuse[37], but also the common method bias: associations between diagnoses acquired from a single source such as the NPR might reflect treatment/diagnostic policies rather than actual relationships between disorders. We partially addressed this issue by including substance use-related criminal convictions from another source in our definition of substance misuse.

Findings from both of our samples consistently suggest that the developmental pathway from childhood mood problems to substance misuse may be different for men and women. The developmental pathways framework includes the concept of equifinality, which denotes that a common outcome such as SUD can develop over time from different starting points.[38] When externalizing symptoms were accounted for, mood problems predicted substance misuse only among women in the CATSS sample. Similarly, the elevated risk of substance misuse in those with anxiety and depressive disorders was explained by comorbid externalizing disorders in men but not in women in the population sample. In both samples, the associations were generally stronger in women. Taken together, our findings suggest that the internalizing pathway to substance misuse may be more prominent in women than in men. However, there was one exception: we found either no association or an inverse association between mood problems/depression and substance misuse in men after adjusting for externalizing disorders at the individual level, yet elevated risk was apparent in within-family analyses. The finding indicates that genetic or shared environmental factors may mask the association between depression and substance misuse in men when co-occurring externalizing disorders are accounted for.

The association between anxiety/mood problems and substance misuse appeared to be partially explained by familial factors in both samples, consistent with other studies indicating SUDs and internalizing disorders sharing etiological factors such as genetic liability and environmental influences.[16-18,36,39,40] These findings highlight the need to take shared underlying liabilities into account when investigating the link between internalizing psychopathology and substance misuse, as the associations seems to at least partially reflect unmeasured genetic and shared environmental factors that affect both traits, and not necessarily a direct effect of internalizing disorders on substance misuse. There was attenuation in the estimates in within-family analyses as compared to the individual level, but as the estimates were often imprecise, strong conclusions cannot be drawn on the role of familial factors. Diagnostic misclassification may also introduce bias which appears as evidence for familial confounding in within-family analyses.[41] Further, as we were unable to conduct separate analyses within MZ and DZ twins due to lack of statistical power, it remains unclear to what extent shared environmental and genetic factors contributed to the familial effects.

Our results also suggested that the effect of comorbidity of internalizing and externalizing psychopathology on substance misuse may depend on sex. In men, externalizing psychopathology without co-occurring internalizing problems was associated with the highest risk of substance misuse. In contrast, comorbidity of internalizing and externalizing psychopathology in women seemed to associate with an especially high risk of substance misuse. These results may reflect sex-specific mechanisms in the development of substance misuse: in women, comorbid externalizing problems appear to amplify the risk of substance misuse in those with internalizing psychopathology. In men, externalizing behavior is central in the development of substance misuse, and internalizing disorders seem to attenuate rather than increase the risk of substance misuse. Our findings are in line with earlier studies

showing a higher risk of substance misuse in "pure" externalizing problems as compared to comorbidity[22], as well as other studies reporting similar risks in comorbid and pure externalizing groups.[23,24] However, it should be noted that some estimates for men and women had overlapping confidence intervals, and thus definite conclusions cannot be drawn.

Our findings imply that in both primary care and specialist services, when a child is referred for an assessment for ADHD or other behavioral problems, additional assessment for comorbid internalizing psychopathology is warranted, because comorbid internalizing and externalizing psychopathology may be associated with an increased risk of alcohol or drug use problems, especially in women. On the other hand, ADHD is often underdiagnosed in girls due to the symptoms being less overt than in boys, and because internalizing psychopathology can overshadow symptoms of ADHD and complicate diagnostic assessment.[42] Underdiagnosing of ADHD could also inflate the association between internalizing disorders and substance misuse, particularly in older birth cohorts where underdiagnosing was more common. Further, mood problems/depression was a risk marker for substance misuse independent of comorbid externalizing problems. Screening for mood-related problems may thus help identifying children who are at risk of developing substance misuse in adolescence or early adulthood. Our findings also emphasize the need to consider how the anxiety phenotype is measured, as the association with substance misuse depended on the severity (clinical diagnosis vs. parental report of symptoms) and type of anxiety disorder.

Several limitations should be noted. First, although the factor structure and neuropsychiatric sub-scales of A-TAC are well validated[31,43], psychometric properties of the mood and anxiety problem scales have not been examined. The mood problems scale includes a variety of symptoms and problematic behaviors and may not capture primarily depression. Parents are also more accurate at identifying externalizing than internalizing symptoms in their children,

which may produce bias.[44] Future studies are encouraged to replicate our study with other measures of mood and anxiety problems. For example, the current study did not include assessments of trauma-related psychopathology, which is associated with subsequent substance use problems.[45]

Second, the present study did not include all cases of SUDs or internalizing and externalizing disorders, because the NPR only captures diagnosed cases among the treatment-seeking population in inpatient and outpatient clinics. Common psychiatric disorders are often treated at the primary care level in Sweden[35], and some individuals do not seek treatment. This is also the reason why the population sample had a higher prevalence of neuropsychiatric disorders than internalizing and externalizing disorders. Individuals with a childhood diagnosis in the NPR are a selected group: children are likely to be referred to inpatient or outpatient psychiatric services either due to a need for neuropsychiatric assessment or because the problem is severe and cannot be treated in primary care. Further, depression and anxiety disorders are generally diagnosed later in life than autism where most cases are diagnosed before adolescence. We aimed to address the possible selection effects by not relying solely on the NPR data in the study but including the CATSS sample as well, and by conducting a sensitivity analysis where we adjusted for autism diagnoses. Our findings were generally similar regardless of the measurement of internalizing disorders, and adjustment for autism had little effect on the results, which increases the confidence that the associations are not due to selection bias. However, autism shares etiological factors with ADHD[46], and did explain a small proportion of the association between internalizing disorders and substance misuse. Further, our results do not necessarily generalize beyond the population of individuals with SUDs with severe enough psychopathology to warrant specialist care, or who were convicted for substance-related offence.

Third, the maximum age at the end of follow-up was 21 or 29 years. Previous studies suggest earlier-onset SUDs to have distinct characteristics as compared to adult-onset SUDs[47], which may also have affected the observed associations in the present study. Finally, the timing of substance misuse and internalizing disorders is another issue to consider, as the first registered diagnosis/conviction date does not correspond well with disorder onset. The analyses of the population sample in particular should be interpreted with this caveat, because it is likely that many individuals without a childhood diagnosis received a diagnosis later in life.

In conclusion, we found evidence of an internalizing pathway to substance misuse in two large cohorts. Mood-related psychopathology in childhood was consistently associated with an elevated risk of substance misuse whereas the relationship of anxiety with substance misuse was complex and depended on the measurement and the type of anxiety disorder. Familial factors partially explained the observed associations. The developmental pattern of substance misuse was different for men and women: internalizing disorders were robustly associated with substance misuse in women only. Further, the role of comorbid externalizing psychopathology seemed to be sex-specific, as externalizing psychopathology amplified the risk for substance misuse more in women than in men.

References

1. Whiteford HA, Degenhardt L, Rehm J, *et al*. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;382(9904):1575-86.
2. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet*. 2009;373(9682):2223-2233.
3. Zucker RA, Heitzeg MM, Nigg JT. Parsing the undercontrol–disinhibition pathway to substance use disorders: A multilevel developmental problem. *Child Dev Perspect*. 2011;5(4):248-255.
4. Hussong AM, Jones DJ, Stein GL, Baucom DH, Boeding S. An internalizing pathway to alcohol use and disorder. *Psychol Addict Behav*. 2011;25(3):390-404.
5. Charach A, Yeung E, Climans T, Lillie E. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. *J Am Acad Child Adolesc Psychiatry*. 2011;50(1):9-21.
6. Erskine HE, Norman RE, Ferrari AJ, *et al*. Long-term outcomes of attention-deficit/hyperactivity disorder and conduct disorder: a systematic review and meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2016;55(10):841-850.
7. Groenman AP, Janssen TW, Oosterlaan J. Childhood psychiatric disorders as risk factor for subsequent substance abuse: A meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2017;56(7):556-569.
8. Fleming CB, Mason WA, Mazza JJ, Abbott RD, Catalano RF. Latent growth modeling of the relationship between depressive symptoms and substance use during adolescence. *Psychol Addict Behav*. 2008;22(2):186-197.
9. Kaplow JB, Curran PJ, Angold A, Costello EJ. The prospective relation between dimensions of anxiety and the initiation of adolescent alcohol use. *J Clin Child Psychol.* 2001;30(3):316–326.
10. Dawson DA, Goldstein RB, Moss HB, Li TK, Grant BF. Gender differences in the relationship of internalizing and externalizing psychopathology to alcohol dependence: Likelihood, expression and course. *Drug Alcohol Depend*. 2010;112(1-2):9-17.

11. Armstrong TD, Costello EJ. Community studies on adolescent substance use, abuse, or dependence and psychiatric comorbidity. *J Consult Clin Psychol*. 2002;70(6):1224-1239.
12. Colder CR, Scalco M, Trucco EM, *et al*. Prospective associations of internalizing and externalizing problems and their co-occurrence with early adolescent substance use. *J Abnorm Child Psychol.* 2013;41:667-677.
13. Pettersson E, Larsson H, Lichtenstein P. Common psychiatric disorders share the same genetic origin: a multivariate sibling study of the Swedish population. *Mol Psychiatry*. 2016;21(5):717-721.
14. Lahey BB, Krueger RF, Rathouz PJ, Waldman ID, Zald DH. A hierarchical causal taxonomy of psychopathology across the life span. *Psychol Bull*. 2017;143(2):142-186.
15. D'Onofrio BM, Lahey BB, Turkheimer E, Lichtenstein P. Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. *Am J Public Health.* 2013;103:46-55.
16. Sihvola E, Rose RJ, Dick DM, Pulkkinen L, Marttunen M, Kaprio J. Early-onset depressive disorders predict the use of addictive substances in adolescence: a prospective study of adolescent Finnish twins. *Addiction*. 2008;103(12):2045-2053.
17. Korhonen T, Huizink AC, Dick DM, Pulkkinen L, Rose RJ, Kaprio J. Role of individual, peer and family factors in the use of cannabis and other illicit drugs: a longitudinal analysis among Finnish adolescent twins. *Drug Alcohol Depend*. 2008;97(1-2):33-43.
18. Edwards AC, Sihvola E, Korhonen T, *et al*. Depressive symptoms and alcohol use are genetically and environmentally correlated across adolescence. *Behav Gen*. 2011;41(4):476-487.
19. Edwards AC, Larsson H, Lichtenstein P, Kendler KS. Early environmental influences contribute to covariation between internalizing symptoms and alcohol intoxication frequency across adolescence. *Addict Behav.* 2011;36(3):175-182.
20. Angold A, Costello EJ, Erkanli A. Comorbidity. *J Child Psychol Psychiatry.* 1999;40: 57-87.
21. Angold A, Costello EJ. Depressive comorbidity in children and adolescents. *Am J Psychiatry.* 1993;150(12):1779-1791.

22. Colder CR, Scalco M, Trucco EM, *et al*. Prospective associations of internalizing and externalizing problems and their co-occurrence with early adolescent substance use. *J Abnorm Child Psychol.* 2013;41:667-677.
23. Miller-Johnson S, Lochman JE, Coie JD, Terry R, Hyman C. Comorbidity of conduct and depressive problems at sixth grade: Substance use outcomes across adolescence. *J Abnorm Child Psychol*. 1998;26:221-232.
24. Capaldi, DM. Co-occurrence of conduct problems and depressive symptoms in early adolescent boys: I. Familial factors and general adjustment at Grade 6. *Dev Psychopathol.* 1991;3: 277-300.
25. Marmorstein NR, Iacono WG. An investigation of female adolescent twins with both major depression and conduct disorder. *J Am Acad Child Adolescent Psychiatry*. 2001;40:299-306.
26. Riggs PD, Baker S, Mikulich SK, Young SE, Crowley TJ. Depression in substance-dependent delinquents. *J Am Acad Child Adolescent Psychiatry*. 1995;34:764-771.
27. Anckarsäter H, Lundström S, Kollberg L, *et al*. The child and adolescent twin study in Sweden (CATSS). *Twin Res Hum Gen*. 2011;14(6):495-508.
28. Ludvigsson JF, Andersson E, Ekbom A, *et al*. External review and validation of the Swedish National Inpatient Register. *BMC Public Health*. 2011;11:450-466.
29. Ekbom A. The Swedish Multi-generation Register. *Methods Mol Biol*. 2010;675,:215-220.
30. Hansson SL, Svanströmröjvall A, Rastam M, Gillberg C, Gillberg C, Anckarsäter H. Psychiatric telephone interview with parents for screening of childhood autism–tics, attention-deficit hyperactivity disorder and other comorbidities (A-TAC): preliminary reliability and validity. *British J Psychiatry*. 2005;187:262–267.
31. Larson T, Anckarsäter H, Gillberg C, *et al*. The autism-tics, AD/HD and other comorbidities inventory (A-TAC): further validation of a telephone interview for epidemiological research. *BMC Psychiatry*. 2010;10:1-12.
32. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol.* 2009;24:659-667.
33. Lahey BB, D'Onofrio BM. All in the family: comparing siblings to test causal hypotheses regarding environmental influences on behavior. *Curr Dir Psychol Sci*. 2010;19:319-323.

34. Lai HMX, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: A systematic review and meta-analysis. *Drug Alcohol Depend*. 2015;154:1–13.
35. Sundquist J, Ohlsson H, Sundquist K, Kendler KS. Common adult psychiatric disorders in Swedish primary care where most mental health patients are treated. *BMC Psychiatry*. 2017;17:234-244.
36. Virtanen S, Kuja-Halkola R. Mataix-Cols D, *et al*. Comorbidity of substance misuse with anxiety-related and depressive disorders: A genetically informative population study of 3 million individuals in Sweden. *Psychol Med*, 2019. Published online 22 July. doi:10.1017/S0033291719001788
37. Merikangas KR, Mehta RL, Molnar BE, Walters EE, Swendsen JD, Aguilar-Gaziola S, Kolody B, Vega WA, Wittchen HU and Kessler RC. Comorbidity of substance use disorders with mood and anxiety disorders: results of the International Consortium in Psychiatric Epidemiology. *Addict Behav*. 1998;23:893–907.
38. Cicchetti D, Rogosch FA. A developmental psychopathology perspective on adolescence. J Consult Clin Psychol. 2002;70(1):6-20.
39. Edwards AC, Aliev F, Bierut LJ, *et al*. Genome-wide association study of comorbid depressive syndrome and alcohol dependence. *Psychiatr Genet*. 2012;22(1):31-41.
40. Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arc Gen Psychiatry* 2003;60:929-937.
41. McGue M, Osler M, Christensen K. Causal inference and observational research: The utility of twins. *Perspect Psychol Sci.* 2010;5:546-556.
42. Quinn PO. Attention-deficit/hyperactivity disorder and its comorbidities in women and girls: an evolving picture. *Curr Psychiatr Rep*. 2008;10(5):419-423.
43. Larson T, Lundström S, Nilsson T, *et al*. Predictive properties of the A-TAC inventory when screening for childhood-onset neurodevelopmental problems in a population-based sample. *BMC Psychiatry*. 2013;13(1):233.
44. Dwyer SB, Nicholson JM, Battistutta D. Parent and teacher identification of children at risk of developing internalizing or externalizing mental health problems: A comparison of screening methods. *Prev Sci*. 2006;7(4):343-357.
45. De Bellis MD. Developmental traumatology: a contributory mechanism for alcohol and substance use disorders. *Psychoneuroendocrinology*. 2002;27:155-170.

46. Ronald A, Larsson H, Anckarsäter H, Lichtenstein P. Symptoms of autism and ADHD: a Swedish twin study examining their overlap. *J Abnorm Psychol*. 2014;123(2):440-451.
47. Clark DB, Kirisci L, Tarter RE. Adolescent versus adult onset and the development of substance use disorders in males. *Drug Alcohol Depend*. 1998;49(2):115-121.

Table 1: Childhood Psychopathology and Substance Misuse in the CATSS Sample and the Population Sample

	Total n (%)	Men n (%)	Women n (%)
CATSS[27]			
Childhood psychopathology			
Mood problems	678 (5.5)	401 (6.3)	277 (4.6)
Anxiety problems	187 (1.5)	101 (1.6)	86 (1.4)
ADHD[a]	599 (4.8)	429 (6.7)	170 (2.8)
Conduct disorder or ODD[b]	304 (2.5)	201 (3.2)	103 (1.7)
Childhood comorbidity			
No childhood psychopathology	11,175 (90.1)	5,623 (88.0)	5,552 (92.2)
Internalizing only	499 (4.0)	254 (4.0)	245 (4.1)
Externalizing only	465 (3.8)	318 (5.0)	147 (2.4)
Both internalizing and externalizing	269 (2.2)	192 (3.0)	77 (1.3)
Substance misuse	411 (3.3)	254 (4.0)	157 (2.6)
Population sample[28]			
Childhood psychopathology			
Depression	1,873 (0.11)	1,103 (0.12)	770 (0.09)
Childhood-specific anxiety disorders	412 (0.02)	231 (0.03)	181 (0.02)
Anxiety disorders	5,300 (0.3)	2,573 (0.3)	2,727 (0.3)
ADHD	60,208 (3.4)	38,915 (4.3)	21,293 (2.5)
Conduct disorders	6,928 (0.4)	4,383 (0.5)	2,545 (0.3)
Autism	19,028 (1.1)	12,552 (1.4)	6,476 (0.8)
Childhood comorbidity			
No childhood psychopathology	1,699,841 (96.1)	865,288 (95.3)	834,553 (97.0)
Internalizing only	5,364 (0.3)	2,516 (0.3)	2,848 (0.3)
Externalizing only	61,476 (3.5)	39,468 (4.3)	22,008 (2.6)
Both internalizing and externalizing	1,835 (0.1)	1,178 (0.1)	657 (0.1)
Substance misuse	102,150 (5.8)	66,137 (7.3)	36,013 (4.2)

Note: CATSS[27]: Total n = 12,408; Men n = 6,387; Women n = 6,021; Population sample[28]: Total N = 1,768,516, Men n = 908,450, Women n = 860,066. Externalizing = exceeding the DSM-IV cut-off of ADHD, ODD, or conduct disorder in the A-TAC in the CATSS sample, and having an ICD diagnosis of ADHD or conduct disorders in the population sample; Internalizing = exceeding the "significant impairment" cut-off of anxiety or mood problems scales in the A-TAC in the CATSS sample, and having an ICD diagnosis of anxiety or depressive disorders in the population sample

[a] Frequencies of individuals exceeding the DSM-IV cut-off in the A-TAC (ADHD symptom scale mean = 1.8 [SD = 2.8])

[b] Frequencies of individuals exceeding the DSM-IV cut-off in the A-TAC (ODD symptom scale mean = 0.5 [1.05], Conduct disorder symptom scale mean = 0.1 [0.4])

Table 2: Hazard Ratios (95% CIs) for the Association of Childhood Anxiety and Mood Problems With Substance Misuse in the CATSS sample

	Anxiety problems	Mood problems
Total		
Individual level		
Minimally adjusted	1.12 (0.51–2.25)	**2.28** (1.69–3.08)
Adjusted for externalizing	0.48 (0.22–1.06)	1.26 (0.87–1.85)
Within-family		
Minimally adjusted	0.80 (0.21-2.98)	**2.67** (1.24-5.74)
Adjusted for externalizing	0.44 (0.11–1.82)	2.16 (0.93–5.00)
Men		
Individual level		
Minimally adjusted	1.58 (0.75-3.32)	**1.96** (1.34–2.90)
Adjusted for externalizing	0.60 (0.25-1.42)	0.99 (0.61–1.60)
Within-family		
Minimally adjusted	1.00 (0.20-4.95)	**3.25** (1.06-9.97)
Adjusted for externalizing	0.52 (0.09-2.87)	2.47 (0.75–8.20)
Women		
Individual level		
Minimally adjusted	0.37 (0.05-2.67)	**2.97** (1.82–4.84)
Adjusted for externalizing	0.22 (0.03-1.57)	**1.86** (1.11–3.11)
Within-family		
Minimally adjusted	0.50 (0.03-8.95)	2.20 (0.76-6.33)
Adjusted for externalizing	0.32 (0.03-3.68)	1.91 (0.64–5.78)

Note: Bolded coefficients indicate the 95% CI does not include 1. Externalizing = Symptoms of ADHD, ODD, and conduct disorder; Minimally adjusted = Adjusted for sex and birth year

Table 3: Hazard Ratios for the Association of Childhood Anxiety and Depressive Disorders With Substance Misuse (95% CIs) in the Population Sample

	Childhood-specific anxiety disorders	Anxiety disorders	Depression
Total			
Individual level			
Minimally adjusted	1.36 (0.87–2.13)	**1.52** (1.35–1.73)	**2.75** (2.36–3.20)
Adjusted for externalizing	**0.56** (0.36–0.89)	0.99 (0.88–1.12)	0.98 (0.85–1.15)
Within-family			
Minimally adjusted	3.34 (0.68–16.47)	1.21 (0.86–1.68)	**2.17** (1.37–3.45)
Adjusted for externalizing	2.75 (0.54–13.97)	0.91 (0.64–1.29)	1.52 (0.93–2.51)
Men			
Individual level			
Minimally adjusted	1.27 (0.72-2.23)	**1.34** (1.12–1.59)	**2.35** (1.93–2.87)
Adjusted for externalizing	**0.51** (0.29-0.90)	**0.80** (0.67–0.96)	**0.77** (0.63–0.94)
Within-family			
Minimally adjusted	NA	1.44 (0.89–2.31)	**3.21** (1.71–6.06)
Adjusted for externalizing	NA	1.01 (0.61–1.65)	**2.35** (1.19–4.62)
Women			
Individual level			
Minimally adjusted	1.55 (0.74-3.26)	**1.77** (1.49–2.11)	**3.65** (2.86–4.64)
Adjusted for externalizing	0.69 (0.33-1.45)	**1.29** (1.08–1.54)	**1.67** (1.33–2.16)
Within-family			
Minimally adjusted	NA	1.01 (0.63–1.62)	1.24 (0.61–2.51)
Adjusted for externalizing	NA	0.81 (0.50–1.34)	0.91 (0.42–1.94)

Note: Bolded coefficients indicate the 95% CI does not include 1. Externalizing = ICD diagnoses of ADHD and conduct disorders; Minimally adjusted = Adjusted for sex and birth year; NA = Model could not be estimated

Figure Titles and Captions

Figure 1: Hazard Ratios (with 95% CIs) for the Association of Childhood Comorbid and Non-Comorbid Psychopathology With Substance Misuse in the CATSS (left) and Population Sample (right)